UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,467	03/01/2004	James M. Mason	52494/2102	2109

26646 7590 11/03/2005

KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/791,467	MASON, JAMES M.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/1/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Election/Restriction

Applicant's election with traverse of Group I, Claims 1-35 and 39-41 in the reply filed on 8/4/05 is acknowledged. Applicant's traverse of the restriction Requirement is persuasive and the Restriction is withdrawn. Claims 1-41 will be examined.

35 USC 102 Rejections

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-6, 8-11, 13-24, 29-31 and 36-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Rother et al.

Applicant and Rother et al. (U.S. Patent 5,871,997, issued 2/16/99, filed 3/6/95, see whole document, particularly Columns 15, 19 and 20 and Examples 1-7) recite methods for preparing stable retroviral vector packaging and producer cell lines for generation of human serum-resistant retroviral vector particles which comprise introducing one or more packaging vectors into a non-primate mammalian cell line (i.e. BHK cells) wherein the cell line exhibits substantially no hybridization to a MoMLV retrovirus probe under stringent washing conditions (the examiner can find no evidence in the art that BHK cells, for example, have endogenous MoMLV viruses or sequences which would hybridize to MoMLV probes under stringent conditions), the cell line is a-

galactosyl positive (i.e. Rother et al. suggests removal of some or most of the a-galactosyl epitopes from the cell surface but nevertheless the cells themselves are inherently a-galactosyl positive), and said cell expresses a cellular targeting protein (i.e. env) and retroviral gag and pol genes in amounts sufficient to package said resistant retroviral particles and wherein a retroviral vector comprising a heterologous gene of choice is introduced into said packaging cells and is packaged into a retroviral particle. Rother et al. also recites a method for transferring heterologous genes into human or primate cells or tissue (i.e. brain cells or tissue) wherein the human serum resistant retroviral vector producing cells (or the particles) are contacted (by oral or aerosol, intravenous, etc. delivery) with the target cells *in vivo* (i.e. in the brain) and the heterologous gene is transferred (See Rother et al., Columns 21-22). With regard to the titers of retrovirus vectors produced (about 10^4 to about 10^8 pfu/ml), these titers are within the normal titers produced from standard retroviral producer cells known in the art (such as BHK cells, evidenced by, for example, Li et al., PNAS, 1996, Vol. 93, pp. 11658-11663) and would be expected (absent evidence to the contrary) from those recited by Rother et al. Rother et al. therefore teaches the claimed invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-6, 8-11, 13-24, 29-31 and 36-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Pensiero et al.

Applicant and Pensiero et al. (U.S. Patent 6,329,199, issued 12/11/2001, priority to 8/14/1994, see whole document, particularly Columns 3, 10-13, Claims 1-8) recite methods for preparing stable packaging and producer retroviral cell lines for generation of human serum-resistant retroviral vector particles (within the titers recited in the claims) which comprise introducing one or more packaging vectors into a non-primate mammalian cell line (i.e. Mv-1-Lu cells) wherein the cell line exhibits substantially no hybridization to a MoMLV retrovirus probe under stringent conditions (the examiner can find no evidence in the art that Mv-1-Lu cells, for example, have endogenous MoMLV viruses or sequences which would hybridize to MoMLV probes under stringent conditions), the cell line is α-galactosyl positive, and said cell expresses a cellular targeting protein (i.e. amphotropic, xenotropic env or VSV G, etc.) and retroviral gag and pol genes in amounts sufficient to package said resistant retroviral particles and wherein a retroviral vector comprising a heterologous gene of choice is introduced into said packaging cells and is packaged into a retroviral particle. Pensiero et al. also recites a method for transferring heterologous genes into human or primate cells or tissue (i.e. brain cells or tissue) wherein the human serum resistant retroviral vector producing cells (or the particles) are contacted (by oral or aerosol, intravenous, etc. delivery) with the target cells *in vivo* (i.e. in the brain) and the heterologous gene is

transferred (See Pensiero et al., Column 11). Pensiero et al. therefore teaches the claimed invention.

Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-14, 16-18, 20-21, 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6,743,631 (hereafter the '631 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite the same methods for generating stable retroviral vector packaging cell lines which produce human serum resistant retroviral particles. The instant claims differ from those of the '631 patent in reciting that the non-primate cell line exhibits substantially no hybridization with a MoMLV retrovirus probe while the '631 patent recites that the cell line exhibits no specific hybridization with a MoMLV gag/pol or env probe. Since the instant claims are broader in this limitation it must be considered that the instant claims

are anticipated by the claims in the '631 patent. With regard to claims 2, 7, 12 and 41, said methods recite a species of the generic claims reading on preparing any stable retroviral vector packaging cell line from a non-primate source; however, since the specification specifically lists the Mpf cell line (ATCC 1656-CRL) as a preferred embodiment, said cell line would have been an obvious choice for use in the claimed method. With regard to the retroviral vector composition claims (Claims 20-21), these claims are drafted in a product-by-process format and would be obvious over the process claims in the '631 patent because said processes are designed to produce the claimed vectors.

35 USC 112, 1st Paragraph Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 7, 12, 15, 19 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A deposit of the Mpf cell line (ATCC Accession Number 1656-CRL) is required since this deposited material is claimed by it's specific ATCC address, i.e. in order to practice the claimed invention the skilled artisan would need unrestricted access to the

specific material deposited at ATCC Accession Number 1656-CRL. Also, the instant specification does not recite a reproducible method for obtaining the Mpf cell line and there is no evidence that said cell line is (and will be) readily available to the skilled artisan for the lifetime of any patent which may issue from the instant application. With regard to the Mv-1-Lu cell line, applicant claims using said cell line for assaying the titers of retroviral vectors produced from the producer cells. The specification does not recite a reproducible method for obtaining said cell line and there is no evidence that said cell line is (and will be) readily available to the skilled artisan for the lifetime of any patent which may issue from the instant application. The Mpf and Mv-1-Lu cell lines are essential for practicing the claimed invention and the deposit requirements for said cells must be satisfied. Applicant is also reminded that the specification must be amended to specify the deposited material, the date of deposit, the correct address of the depository, etc. and if the deposit is made after the filing date of the application, section 37 CFR 1.804(b) must be complied with (See 37 CFR 1.801-1.809).

Claims 25-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant claims methods of transducing a cell with a human serum resistant retroviral vector in the presence of a body fluid which comprises administering the

recited retroviral vectors or non-primate packaging cell lines which produce said vectors to said cells *in vivo* or *ex vivo*. Applicant also specifically claims gene therapy methods of treating diseases and pharmaceutical compositions comprising said retroviral particles and a pharmaceutically acceptable carrier. Since the only recited use for the claimed methods of transducing cells, in the presence of body fluids, with the recited retroviral vectors is for gene therapy, said claims will also be examined as reading on gene therapy methods.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reaches by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following: 1) Unpredictability of the art. The gene therapy art is highly unpredictable. The unpredictability is manifested in virtually all aspects of gene therapy. The primary areas of unpredictability involve delivery of the vectors to the appropriate tissues, targeting of the vectors to the appropriate cells, the transient and unpredictable expression of the transgene in cells *in vivo* and the lack of suitable animal models of human diseases where results of potential gene therapy treatments can be extrapolated to humans. Specifically, with regard to retroviral vectors, additional problems exist with regard to random integration of the vector nucleic acid into the cellular genome with the

associated possible disruption of normal genes, activation of oncogenes, transgene promoter silencing by adjacent chromosomal sequences, poor efficiency of transfection of target cells *in vivo*, poor efficiency of transduction of pseudotyped retroviral vectors *in vivo*, etc. Indeed, at present all U.S. clinical studies using retroviruses as gene therapy agents are on hold due to the possibility that retroviral vectors may result in leukemia in patients treated with the vectors (See Marshall, Science, 2003, Vol. 299, No. 5605, p. 320). For reviews of the unpredictability of gene therapy techniques, see Mountain, TIBTECH, 2000, Vol. 18, pp. 119-128; Kmiec, American Scientist, 1999, Vol. 87, pp. 240-247) Anderson, Nature, 1998, Vol. 392, pp. 25-30; Verma et a1., Nature, 1997, Vol. 389, pp. 239-242; Paillard, Human Gene Therapy, 1998, Vol. 9, pp. 767-768; Fox, Nature Biotechnology, 2000, Vol. 18, pp. 143-144; Goncalves, BioEssays, 2005, Vol. 27, pp. 506-517, etc.

2) State of the art. At the time of filing of the instant application, no successful gene therapy protocols had been unambiguously demonstrated to be successful.

3) Number of working examples. Applicants present no working examples of the claimed invention.

4) Amount of guidance presented by applicants. Applicants present generic guidance on administering the retroviral vector producing cells to animals or humans. Applicants however present no guidance on how the skilled artisan would overcome the art recognized problems associated with successful practicing of gene therapy using retroviral vectors.

5) Nature of the invention. The invention involves one of the most complex and unpredictable areas of molecular biology/medicine; the use of viral gene therapy vectors to treat disease in humans.

6) Level of skill in the art. The level of skill in the art is high; however, given the unpredictable nature of the art, the poorly developed state of the art, the lack of guidance provided by applicants and lack of working examples, the skilled artisan would have needed to have conducted trial and error experimentation in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have needed to conduct undue and excessive experimentation in order to practice the claimed invention.

It is noted that this Office Action contains rejections of the same claims under 35 USC 112, 1st (enablement) and 35 USC 102(b) and (e). While these rejections may seem contradictory, they are not because each is based upon a different legal analysis, i.e. sufficiency of the disclosure of the instant application to support claims under 35 USC 112, 1st paragraph vs. sufficiency of a prior art disclosure to anticipate or render obvious an embodiment(s) of the claimed invention (See *In re Hafner*, 161 USPQ 783 (CCPA 1969)).

35 USC 112, 2nd Paragraph Rejections

Claims 1-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and dependent claims) are vague in the recitation of the phrase "exhibits substantially no hybridization to a Moloney-MLV retrovirus probe under stringent washing conditions". First, the term "substantially no hybridization" is unclear since "substantially" is a relative term with no frame of reference for comparison, i.e. substantially no hybridization compared to what standard? It is unclear what level of hybridization would be included within this limitation and what level would be excluded. Second, it is unclear what type of "probe" is being referred to, i.e. a retrovirus probe could be 10 nucleotides in length or the size of the entire MoMLV genome and the hybridization one would expect would vary depending on the size of the probe. Therefore, it is unclear what cells would be included within the claim language and accordingly the metes and bounds of the claimed subject matter are unclear. Third, the claim is unclear since "stringent washing conditions" have not been identified in the specification and these conditions would be expected to vary depending on the definition of the subjective term "stringent".

Miscellaneous

In Claim 6, line 1, deletion of the "a" prior to the word "stable" is suggested because the article "a" does not agree with the plural "producer cells".

Claims 6, 11 and 16 recite the "packaging cell of claim 1" or the "producer cells of claim 6". However, claims 1 and 6 are method claims, not composition claims. For clarity purposes, it is suggested that claim 1 and 6 be amended to recite "introducing a retrovirus vector into the packaging cell line produced by the method of claim 1". Claim 16 should be amended to recite "culturing the producer cells produced by the method of claim 6".

Claim 20 is dependent upon claims 11, 12, 16 or **41**. A claim cannot depend from a later numbered claim. The claim dependency must be changed prior to allowance so that the claim depends from an earlier numbered claim.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
October 23, 2005

DAVID GUZO
PRIMARY EXAMINER